

REMARKS

I. Status of the Application

Upon entry of the claim amendments, 16-25, 27-28, 30-31, 33, and 35 are pending. Without prejudice or disclaimer, Applicants amend claim 16 to recite dye staining, and to cancel several claims reciting Western blotting. Other changes merely re-phrase the claims. Applicants amend claim 16 to place the claim into active rather than passive voice for better readability. Applicants also amend claim 31 to depend from claim 17 rather than from claim 30, and amend claim 33 and 35 to recite "visualization" instead of "staining." Applicants respectfully request entry of the amendments according to 37 C.F.R. § 1.114.

Applicants also request entry of the Replacement Drawings previously submitted in the Amendment filed December 20, 2005. Applicants do not re-submit those drawings here, as it is Applicants' understanding that the Office should not need further copies. However, if this is not the case, Applicants will send a new set of drawings at the Office's request.

II. Objection to the Drawings

The Office Action of September 20, 2005, included an objection to the replacement black-and-white drawings previously submitted on July 25, 2005. (Office Action at pages 2-3.) To advance prosecution of this application, on December 20, 2005, Applicants re-submitted all of the replacement drawings for Figures 1-9 previously filed on July 25, 2005, and respectfully request the Office to re-scan and enter the drawings if it has not done so already.

The Examiner further believes that those replacement drawings were intended to be color drawings and requests Applicants to submit the required petition and fee for color drawings. (Office Action at pages 2-3.) However, the replacement drawings, like the original drawings in this application, are black-and-white drawings. While the replacement drawings contain photographic images, those images are in greyscale. Hence, Applicants are confused by the Examiner's remarks about color drawings.

The Examiner also objects to Figure 8, stating that it has "poor resolution" and is "unreadable." Applicants agree that the resolution of Figure 8, after it was scanned into the Office's public PAIR database, is of very poor quality in comparison to the replacement Figure 8 that Applicants submitted to the Office. The replacement of that figure should correct the resolution problem.

Accordingly, Applicants request the withdrawal of this objection.

III. The Claims Are Definite under 35 U.S.C. § 112, Second Paragraph

The Office continues to reject several claims as allegedly indefinite. (Office Action at pages 3-5 and 9-10.) Applicants again traverse those rejections. Applicants respectfully submit that the Office is applying far too strict a standard in this case. Further, the Office does not consider the claims in light of the application's disclosure as a whole and the knowledge of one of ordinary skill in the art, as the Office is required to do under 35 U.S.C. § 112. Nor does the Office suggest any correction to the claim language to assist Applicants, as the M.P.E.P. recommends. M.P.E.P. § 2173.02.

Indeed, the M.P.E.P. points out that claims need only define the patentable subject matter with a degree of particularity and distinctness that is reasonable, and not exact. (M.P.E.P. § 2173.02, emphasis in original.) The M.P.E.P. also emphasizes that

it is improper to consider the definiteness of the claims "in a vacuum." (*Id.*) Instead, claim terminology must be analyzed in light of (a) the application's disclosure, (b) the prior art, and (c) the understanding of those of ordinary skill in the art. (*Id.*) Therefore, the M.P.E.P. stresses that "[a]pplicants are given a great deal of latitude" in their choice of language. (See M.P.E.P. § 2173.05(e).) Further, a lack of antecedent support from the earlier claim language or specification taken alone is not sufficient to warrant a rejection under § 112, second paragraph. (M.P.E.P. § 2173.05(e); emphasis added.)

Claim 16

The Office continues to object to numerous terms or phrases used in independent claim 16. (Office Action at pages 3 and 8-9.) Applicants traverse all of those rejections, and address each phrase in turn below. Applicants further submit that the claims are clear on their face and accordingly request the withdrawal of all of the rejections discussed below.

1. "multimer bands"

The Office contends that "multimer bands" lacks antecedent basis. Applicants note that this term was previously preceded by the article "the," but the claim was amended on July 25, 2005, to remove the article. Further, the term "the multimer bands" appears in original claim 1 of the application. Yet the Office still rejects claim 16.

Again, Applicants remind the Office that a lack of antecedent support is not sufficient to warrant a § 112, second paragraph, rejection. (M.P.E.P. § 2173.05(e); emphasis added.) Claim 16 is drawn to a method involving "gel electrophoresis." Indeed, the point of performing gel electrophoresis is to obtain size, shape or charge-separated "bands" of whatever molecule is being studied. Hence, Applicants submit

that it would be quite clear to one of ordinary skill in the art that electrophoresis performed to "determine the multimers" of a "multimer-forming protein" would result in "multimer bands," (i.e. bands representing those multimers). This is especially the case given that examples of the "multiple bands" resulting from electrophoresis of multimer-forming proteins are described throughout the application and are depicted in many of the figures.

2. "multimer bands are visualized by immunostaining after a Western blot analysis"

The Office contends that this phrase also renders claim 16 indefinite because "[t]he purpose of immunostaining a blotted gel is not clear." (Office Action at page 3.) This rejection is moot in light of the amendments to claim 16. In any event, Applicants submit that the entire phrase is clear on its face.

3. "submarine electrophoresis"

The Office again rejects this term (Office Action at pages 4 and 9), although Applicants have previously explained on record that "submarine" modifies "electrophoresis."

Moreover, Applicants respectfully submit that the Office's confusion would be alleviated by examining the disclosure as a whole and considering the knowledge of those of ordinary skill in the art as the M.P.E.P. specifically directs. M.P.E.P. § 2173.02. First, the Office takes the "hoagie-like sandwich" idea out of context. (Office Action at page 4.) The "blot sandwich" described at page 9, line 9, does not even relate to electrophoresis but to Western blotting. Second, the "catamaran like" weighting of a gel that the Office refers to, and which is discussed at page 5, line 37, refers to attempts in the prior art to jerry-rig a conventional agarose gel apparatus by placing weights at each

side of the gel to prevent it from floating on the surface of the buffer. (See page 5, line 29, to page 6, line 2.) In the next paragraph, the specification states that this and other problems can be solved by using "submarine electrophoresis using a continuous, homogeneous agarose gel free of lumps . . ." (Page 6, lines 4-15.) In addition, the application includes an example submarine electrophoresis procedure at page 7, lines 6-26, in which the buffer is re-circulated with a pump and maintained at fairly constant temperature. Hence, those of ordinary skill reading this application would understand the metes and bounds of "submarine electrophoresis."

4. "visualized by immunostaining"

The Office also objects to this phrase stating that "it is not clear whether/how "immunostaining" is incidental to "visualized." (Office Action at page 4.) This rejection is moot due to the amendment to claim 16, though Applicants submit that the phrase is clear on its face.

5. "by immunostaining after a Western blot analysis"

The Office objects to this term, stating that "it is not clear whether the step of "immunostaining" is completed during and/or prior to the step of fractionation by submarine electrophoresis. (*Id.*) This rejection is also moot in light of the amendment to claim 16.

6. "using a specific antibody-enzyme conjugate"

The Office objects to this term stating that "it is not clear whether said antibody-enzyme conjugate is used during both immunostaining and Western blot analysis." (*Id.*) This rejection is also moot in light of the amendment to claim 16.

7. "optionally"

The Office objects to this term, contending that it isn't clear whether the steps that follow the word are optional or required. (*Id.*) Applicants submit that the word "optionally" means clearly that those steps are "optional." If they were required, there would be no need to call them optional. Thus, this limitation is clear on its face. Moreover, the M.P.E.P. explains that "the language 'containing A, B, and optionally C' [is] considered acceptable alternative language because there [is] no ambiguity as to which alternatives are covered by the claim." M.P.E.P. § 2173.05(h) citing *Ex parte Cordova*, 10 USPQ2d 1949 (Bd. Pat. App. & Inter. 1989); *Ex parte Wu*, 10 USPQ2d 2031 (Bd. Pat. App. & Inter. 1989). Claim 16 is drafted in that acceptable format.

In summary, Applicants traverse all of the above rejections and submit that claim 16 is definite. Accordingly, Applicants request the withdrawal of each rejection above.

Claim 29

1. "the agarose gel employed for the Western blot analysis"

The Office contends that this phrase lacks antecedent basis. (Office Action at page 5.) This rejection is moot as claim 29 is canceled herein..

2. "chosen from"

The Office asserts that the phrase "chosen from" is indefinite and contends that it should be re-drafted as "selected from the group consisting of." (*Id.*) This rejection is also moot in light of the cancellation of claim 29, however, Applicants note that phrases such as "selected from" and "chosen from" prior to a list of species represent definite claim language.

Claims 31-32 and 35

The Office rejects those claims due to the terms "after blue staining," "after immunostaining," and "prior to the staining." The Office contends that those terms result in a "comparative type mismatch in claim 16." (Office Action at page 5.) Applicants note that the rejection is moot as to "after immunostaining" because claim 32 is now cancelled.

Applicants respectfully do not understand what the Office means by a "comparative type mismatch." But Applicants believe the Office is contending that the timing of the staining steps here and the electrophoresis separation of claim 16 is not clear, as the Office contends with respect to the "by immunostaining after a Western blot analysis" phrase of claim 16, discussed above. However, because one cannot meaningfully analyze a stained gel until after the electrophoresis procedure, Applicants submit that the claims are clear on their face and need no further amendment. Hence, Applicants request that this rejection be withdrawn.

Claim 35

The Office contends that the term "prior to the staining" lacks antecedent basis. Solely to speed prosecution, Applicants amend the claim to recite "before the visualization." This renders the rejection moot, and Applicants request its withdrawal.

IV. Claims 16, 19-26, 30, 32, and 34 Are Novel over Krizek & Rick

The Office next contends that an article by Krizek & Rick teaches a determination of von Willebrand factor using a continuous agarose gel and a blotting membrane immunostained with an antibody-enzyme conjugate dye, referring to sections 1.2 and 1.7 of the article. (*Thromb. Res.* 97: 457 et seq. (2000); Office Action at pages 5-6.)

Applicants traverse this rejection and submit that the Office has not made a *prima facie* case of anticipation against any of the above claims.

According to the M.P.E.P. “[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” M.P.E.P. § 2131. Furthermore, the courts require the Office to base rejections under § 102 with substantial evidence or fact based reasoning showing why the Office believes that each and every element is actually present in the teachings of the reference. M.P.E.P. § 2112(V); *In re Lee*, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002); *In re Zurko*, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001). In particular, the Office cannot support a claim rejection over the prior art on conclusory statements, but must set forth the fact-based rationale upon which it relies. *Lee*, 61 U.S.Q.Q.2d at 1434-5. Hence, the burden remains on the Office to explain why it concludes that all of the elements of Applicants' claims appear in Krizek & Rick.

In addition, the Office rejects claims 20-25 over Krizek & Rick under § 102, but then asserts that “it would have been obvious” to one of ordinary skill in the art to modify the temperature ranges and agarose concentrations and cites a court case (*In re Aller*, 105 U.S.P.Q. 233 (C.C.P.A. 1955)) that concerns § 103 and not § 102. Thus, this rejection under § 102 is improper, as the Office admits that Krizek & Rick do not teach all of the elements of those claims as required for a *prima facie* case under § 102. It appears to Applicants that the Office intended to reject claims 20-25 under § 103 rather than § 102. Hence, Applicants address those claims below in the section V, part 3, of this amendment.

While the Office has not met its burden to establish a *prima facie* case of anticipation, Applicants point out to speed prosecution that Krizek & Rick's system does not use either a "dye in the gel" for visualization or a "continuous, homogeneous agarose gel free of lumps." Indeed, all of Krizek & Rick's figures use show that their gels were uneven and contained lumps, because of the obvious distortions visible in the bands. See, for example Figure 1 at page 459, in which the bands appear as uneven waves rather than straight lines, and also Figures 2 and 3, in which further waves can be seen within the bands and in which the bands contain characteristic twists or "smiles." Such distortions are hallmarks of gels that are non-homogeneous and contain lumps. In contrast, note that Applicants' gel bands are generally even and straight, and lack the strongly visible distortions seen in those of Krizek & Rick. (See Figures 1-9 as re-submitted herein.)

The Office contends that the distortions in Krizek & Rick's figures could be the result of photocopying. (Office Action at page 11.) However, the Office overlooks that the distortions in those figures include waves and smiles in the bands that are too large to be photocopying artifacts. Nevertheless, Applicants are happy to request a re-print of the article from *Thrombosis Research* for the Examiner should he require photographic-quality versions of those figures for comparison to Applicants' figures.

For that reason alone, the Krizek & Rick article cannot anticipate Applicants' claims, and Applicants request the withdrawal of this rejection.

V. All of the Claims Are Non-Obvious over the Cited Art

1. Rejection of Claims 16-27 and 30-34 over Connaghan et al. in view of Krizek & Rick

The Office maintains the rejection of claims 16-27 and 30-34 over Connaghan et al. (*Blood* 65: 589 (1985)) in view of Krizek & Rick, discussed in the preceding section. (Office Action at page 6.) Applicants continue to traverse that rejection.

A *prima facie* case of obviousness must satisfy three requirements. See M.P.E.P. § 2143. First, the cited references teach or suggest each and every limitation of the claims. Second, there must be a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine their teachings and, third, a reasonable expectation of success in performing the combination. Both the motivation and the expectation of success must also be found in the references themselves or in the knowledge generally available to one of ordinary skill in the art; not in the application being examined. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); M.P.E.P. § 2142. Accordingly, the references must be viewed without the benefit of hindsight afforded by the claimed invention. M.P.E.P. § 2141. This combination fails all three of those requirements.

Connaghan and Krizek & Rick Do Not Teach All of the Claim Elements

Again, the Office relies on Connaghan for “qualitative and quantitative electrophoretic determination of von Willebrand factor and fibrinogen using a continuous agarose gel stained with a suitable dye.” (Office Action at page 6.) The Office relies on Krizek & Rick for teaching detection of von Willebrand factor by a Western blot. (*Id.*)

First, the Examiner apparently contends that both Figures 1 and 2 of Connaghan show dye staining of multimer bands. (Office Action at page 11; Advisory Action at page 2.) However, Applicants respectfully note that this is incorrect. While Connaghan

does use a dye in a couple of lanes in one of its gel figures, Connaghan uses radioactive labeling to detect and quantify multimer bands.

Specifically, in Figures 1 and 2, to which the Examiner refers, the only lanes that show staining with dyes are the lanes in Figure 1 marked "C.B." for Coomassie blue. (Office Action at page 11; Advisory Action at page 2.) All of the other lanes in Figure 1 and all of Figure 2, as well as all of Figures 3-8, show bands visualized by radio-labeling, which is significantly more sensitive than dyes, as Connaghan itself points out. (See the legends to Figures 1 and 2 and see Connaghan at page 591, column 1.) Indeed, comparing the lanes in Figure 1 marked "C.B." for Coomassie blue to those marked "A.R." for autoradiography, it is evident that the Coomassie blue-stained lanes cannot effectively detect multimers of von Willebrand protein and fibrinogen in Connaghan's experiments. Generally only one or two bands are visible in those lanes compared to the ladder of bands seen with radio-labeling. (Compare the lanes in Figure 1 and see also Figures 2-8.) Connaghan comments that, in contrast to the dye-stained gel, "[t]he autoradiogram of the same gel strip was more sensitive . . . and additional bands were noted that correspond to higher polymers." (Connaghan at page 591, column 1; and see Figures 1-4 and 6-8.)

Hence, one of ordinary skill in the art reading Connaghan would conclude that dyes should not be used to visualize multimer bands. For that reason, the article strongly teaches away from "visualizing" bands "by a dye in the gel" as Applicants claim. Connaghan also does not teach quantitating dye-stained gels; only radioactively labeled samples were quantitated. Krizek & Rick does not bridge the gap left by Connaghan

because it does not teach or suggest staining using a "dye in the gel," as Applicants' claims require.

In addition, Applicants previously pointed out that neither reference teaches a "submarine electrophoresis [procedure] using a continuous, homogeneous agarose gel free of lumps" as Applicants claim. The cited articles, in contrast, simply teach standard horizontal gels which have a tendency to float on the surface of the buffer, as pointed out in the paragraph bridging pages 5-6 of Applicants' specification. Also, as discussed above, it is evident from the figures of Krizek & Rick, for instance, that its gels contain lumps or uneven polymerization, or that they are deformed during electrophoresis, because several of the lanes of bands are unevenly stained. Hence, those gels are not "homogeneous" and "free of lumps" as Applicants' claims require.

In summary, neither Connaghan nor Krizek & Rick teach all of the claim elements. For that reason alone this rejection is not a *prima facie* case of obviousness. But the articles fail the other two requirements of obviousness as well.

There is No Motivation to Combine Connaghan with Krizek & Rick

Applicants reiterate that in order to support a motivation to combine references, "it is incumbent upon the Office to identify some suggestion to . . . make the modification." *In re Mayne*, 104 F.3d at 1342, citing *In re Jones*, 958 F.2d 347, 351 (Fed. Cir. 1992). The mere fact that the references **can** be combined or modified does not itself render the combination obvious. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Instead, motivation to combine requires a teaching that the combination is **desirable**, not just that it is feasible. *Winner v. Wang*, 53 U.S.P.Q.2d

1580, 1590 (Fed. Cir. 2000). In addition, references that teach away from the instant invention may alone defeat a claim of obviousness. *Id.*

First, because Connaghan's Coomassie-stained gels were not effective, and because Krizek & Rick do not teach visualizing multimer bands with a dye in the gel, there is no motivation to combine those two articles so as to obtain Applicants' claim 16. Indeed, taken together, they suggest that one should not use dyes to visualize multimers but should use a more sensitive method of staining and that dyes such as Coomassie are ineffective.

In addition, there is no teaching in either Connaghan or Krizek & Rick of using a "submarine electrophoresis using a continuous, homogeneous agarose gel free of lumps." The Krizek & Rick paper seems satisfied with the uneven bands and lumps that appear in its Figures 1 and 2, and accordingly provides no motivation to change the procedure to avoid them. Thus, the two papers do not provide any objective teaching that would make it desirable to use "submarine electrophoresis" with an agarose gel that is "homogeneous" and "free of lumps," and to visualize the bands in such a gel by dyes or immunostaining, as all of Applicants' claims expressly require. Instead, the teachings of those two articles would lead one of ordinary skill in the art down a different path to that which Applicants took: continuing to use non-homogeneous gels and labeling with radiolabels.

There is No Reasonable Expectation of Success

Finally, if one were, solely for the sake of argument, to combine the teachings of Connaghan and Krizek & Rick, Applicants re-emphasize that there would be no reasonable expectation of success in "visualizing" multimers "by a dye in the gel" after a

"submarine electrophoresis" procedure. For example, Connaghan suggests in its Figure 1 that Coomassie blue staining was too insensitive to effectively reveal multimer bands in the gels. (Compare the two lanes at the far left of Figure 1 of Connaghan marked "A.R." for autoradiography and "C.B." for Coomassie blue.) Krizek & Rick does not address this issue because it does not show staining with a "dye in the gel."

In summary, this combination of publications fails all three requirements for a *prima facie* case of obviousness, and Applicants respectfully request the withdrawal of this rejection.

2. Rejection of Claims 28-29 over Connaghan et al. in view of Krizek & Rick and Riley & Provonchee

The Office also rejects claims 28-29 over Connaghan et al. and Krizek & Rick and further in view of Riley & Provonchee. (Office Action at page 7; U.S. Patent No. 6,090,255.) (The rejection is moot as to canceled claim 29.) As Applicants point out above, the combination of Connaghan and Krizek & Rick fails all three of the requirements for a *prima facie* case of obviousness.

Riley & Provonchee does not overcome the deficiencies in Connaghan and Krizek & Rick because it relates merely to methods of packaging and protecting gels from damage during shipment and storage. It does not teach specific methods of using gels or performing electrophoresis. Hence, claim 28 is non-obvious and Applicants request the withdrawal of this rejection.

3. Rejection of Claims 20-25 over Krizek & Rick (see section above)

The Office also rejects claims 20-25 over Krizek & Rick as part of the rejection discussed above under 35 U.S.C. § 102(b). (Office Action at pages 5-6.) However, as Applicants previously noted, the Office referred to standards of obviousness rather than

anticipation in discussing those claims, suggesting that the Office meant to reject them under § 103 rather than § 102. Accordingly, Applicants address that rejection here.

Applicants traverse the rejection because Krizek & Rick do not teach or suggest all of the elements of Applicants' claims as required for a *prima facie* case of obviousness. As discussed above, Krizek & Rick does not teach dye staining as claimed. Further, it is clear from the figures of Krizek & Rick that its gels contain lumps or uneven polymerization because of the wavy and distorted bands appearing in all of the 3 figures in that paper. Hence, Krizek & Rick does not teach visualization "by a dye in the gel" and also do not teach "using a continuous, homogeneous agarose gel free of lumps." Nor does that paper suggest that there is any deficiency in the gels that it does use to offer an objective motivation or desire to improve the method. Hence, Krizek & Rick cannot make any of claims 20-25 obvious and Applicants request the withdrawal of this rejection.

4. Rejection of Claims 28-29 over Krizek & Rick in view of Riley & Provonchee

Finally, the Office rejects claims 28-29 over Krizek & Rick in view of Riley & Provonchee. (Office Action at page 7-8; again, the rejection is moot as to canceled claim 29.) As discussed previously, Krizek & Rick does not teach "visualizing multimer bands by a dye in the gel," does not teach "using a continuous, homogeneous agarose gel free of lumps," and provides no objective motivation for one of ordinary skill in the art to make such a dye-stained gel. Riley & Provonchee does not fill that gap in Krizek & Rick because it relates merely to methods of packaging and protecting gels from damage during shipment and storage. It does not teach specific methods of using gels

or performing electrophoresis. Hence, claim 28 is non-obvious and Applicants request the withdrawal of this rejection.

CONCLUSION

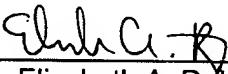
In view of the foregoing remarks, Applicants request the entry of this Request for Continued Examination and Amendment under 37 C.F.R. § 1.114, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any required fees that are not found herewith to deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: February 21, 2006

By: 
Elizabeth A. Doherty
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Attachments:

RCE Form

Petition for a Two-Month Extension of Time to February 21, 2006